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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,360	12/21/2006	Paul J. Hergenrother	ILL01-009-US	8169

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EVAN LAW GROUP LLC
600 WEST JACKSON BLVD., SUITE 625
CHICAGO, IL 60661

EXAMINER	
BLAND, LAYLA D	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,360	HERGENROTHER ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-39* is/are pending in the application.

4a) Of the above claim(s) *25-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/US04/34010, filed October 14, 2004, which claims benefit of 60/510,916, filed October 14, 2003.

Applicant's amendment submitted January 4, 2008, wherein claims 1-17 and 40-53 are canceled and claims 18, 25, and 33 are amended is acknowledged. Applicant's election with traverse of Group V, claims 18-24 in the reply filed on January 4, 2008 is acknowledged. The traversal is on the ground(s) that, as amended, all the claims share a common technical feature, a method of measuring activity of an NAD+ utilizing enzyme, as specified in claim 18. Groups V-VII, remaining after the amendment of January 1, 2008, are drawn to different methods comprising different method steps. Group VI requires measuring activity of an enzyme with and without a compound and then comparing the results, which is not required by Group V. Group VI requires measuring activity of an enzyme with a patient and comparing with a control enzyme, which is not required by Group V. Furthermore, claim 18 is not novel, as will be discussed below, and thus is not a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-39 are pending. Claims 25-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 4, 2008.

Claims 18-24 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

Factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application include actual reduction to practice, disclosure of drawings or structural chemical formulas, sufficient relevant identifying characteristics, method of making the claimed invention, level of skill and knowledge in

the art, and predictability in the art. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to methods of measuring activity of an NAD+ utilizing enzyme, comprising incubating the enzyme with NAD+ and a substrate for the enzyme, converting any remaining NAD+ to a fluorescent compound, and measuring the amount of fluorescence of the fluorescent compound. Only methods wherein the enzyme is PARP and the fluorescent compound is compound 1 have been reduced to practice. The instant claims encompass any enzyme which utilizes NAD+, including those not yet known in the art. Likewise, substrates including those not yet known in the art are included in the scope of the claims. However, disclosure of enzymes other than PARP, substrates for those enzymes, and fluorescent compounds other than compound 1 have not been provided by drawings, structural formula, or sufficient relevant identifying characteristics. Furthermore, methods of obtaining enzymes other than PARP, substrates for those enzymes, and fluorescent compounds other than compound 1 are not disclosed.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 18-24 are broad and generic, with respect to all possible enzymes and substrates and/or fluorescent derivatives encompassed by the claims. The possible variations are limitless to any enzymes, substrates, and/or fluorescent derivatives. The specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of one enzyme (PARP), a number of

substrates for PARP (but not for other enzymes), and one fluorescent derivative (compound 1), the specification does not provide sufficient descriptive support for the myriad of enzymes, substrates, and fluorescent derivatives embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recite the limitation "an NAD+ utilizing enzyme," "a substrate for the enzyme," and "a fluorescent compound." Neither the specification nor claims 18-23 define which enzymes are intended and the skilled artisan would not be apprised of the metes and bounds of the claim. Likewise, the skilled artisan would not be aware of

which compounds could be considered substrates for NAD+ utilizing enzymes, especially for those enzymes which have not been identified. Neither the specification nor claims 18 or 24 define which fluorinated derivatives are encompassed by the claim and the skilled artisan would not be aware of which modifications to NAD+ are intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Weetall (US 4,166,765, September 4, 1979, PTO-1449 submitted August 8, 2007).

Weetall teaches that bacteria of the genus Neisseria can be detected by testing for the presence of an enzyme capable of oxidizing 1,2-propanediol and reducing NAD [see abstract]. The method comprises incubating a lysate of body fluid in the presence of 1,2-propanediol and NAD; NAD is reduced to NADH, which is observed fluorometrically [column 1, line 60 - column 2, line 2]. It is noted that claim 18, given the broadest reasonable interpretation, does not require the method steps to be done in any particular sequence and thus they can be done simultaneously. Thus, "any remaining NAD+" is any NAD+ which is present in the sample, and claim 18 is anticipated by Weetall.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (Analytical Biochemistry 68, 54-61 (1975), PTO-1449 submitted August 8, 2007) in view of Osawa et al. (Journal of clinical Microbiology, Apr 1997, p. 951-953), as evidenced by Nakamura et al. (Analytical Chemistry, vol. 50, No. 14, December 1978, PTO-1449 submitted August 8, 2007).

Clark et al. teach that NAD+ can be detected after being converted to a fluorescent compound by treatment with acetophenone in KOH followed by formic acid [page 61, Discussion].

Clark et al. do not teach detection of NAD+ in the presence of an enzyme.

Osawa et al. teach a method which uses NAD degradation as a biochemical marker for identifying CT-producing *V. cholerae* O1 and O139. CT subunit A has NADase activity. [page 951, first two paragraphs]. After incubation of seven strains of *V. cholerae* with NAD solution in PBS, the concentration of NAD remaining in each well was measured by color [page 951, Development of an assay system]. Wells containing NAD at more than 80 umol/liter gave a distinct red color, while the ones containing NAD at a concentration of less than 30 umol/liter gave only a faint pink color [page 952, first full paragraph].

Nakamura teaches that acetophenone has been used for fluorimetric determination of NAD+. The procedure involves reaction of NAD+ and acetophenone in alkaline media and successive heating with excess acid which produces fluorophores [page 2047, second paragraph]. The mechanism of the reaction is shown in Scheme 1 [page 2047]. Scheme 1 shows that reaction of NAD+ and acetophenone produces compound 1 of the instant claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Clark et al. for measuring activity of a NAD+ utilizing enzyme. Measuring the activity of an NAD+ utilizing enzyme via measurement of NAD+ is known in the art, as taught by Osawa, and the skilled artisan could easily conceive of using Clark's method of measuring NAD+ for the same purpose. Nakamura is cited to establish that the method of Clark et al. produces compound 1 of the instant claims.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark in view of Osawa, as evidence by Nakamura, as applied to claims 18-23 above, and further in view of Pieper et al. (PNAS, February 15, 2000, vol. 97, no. 4, 1845-1850).

Clark and Osawa teach as set forth above, fluorometric measurement of NAD+ for measuring the activity of an NAD+ utilizing enzyme.

Clark and Osawa do not teach measurement of the activity of PARP.

Pieper et al. teach that Poly(ADP-ribose) polymerase-1 (PARP-1) catalyzes polymerization of ADP-ribose from its substrate NAD+. Through PARP activation,

NAD+ is substantially reduced. [page 1845, first paragraph]. Basal *in vivo* neuronal PARP activity is diminished and basal NAD+ levels are elevated after treatment with NMDA-R antagonists, free radical scavengers, and nNOS inhibitors [page 1845, third paragraph].

It would have been obvious to one skilled in the art at the time the invention was made to carry out the method as described above, for measuring the activity of PARP. PARP utilizes NAD+, as does CT subunit A, and the correlation between NAD+ concentration and PARP activity is established by Pieper. Thus, the skilled artisan could easily conceive of using Clark's method of measuring NAD+ for measuring the activity of PARP.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Tuesday - Friday, 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623